Soluble polymer supported asymmetric synthesis (SPSAS)\textsuperscript{8}

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Role of asymmetric catalysis in solid phase organic synthesis is described especially on the soluble polymer supports, namely, poly(ethylene glycol). The review focus only on the recent progress in this area. Some of advantages as well as limitations posed by this soluble polymer system is also described. The popular reactions covered in this review include asymmetric dihydroxylation, epoxidation, reductions and C-C bond formations.

Combinatorial technology was originally developed as a method for constructing vast arrays of peptides for screening against receptor and antibody interactions. Drug discovery has traditionally relied upon optimisation of lead structures usually obtained from biological sources through a time consuming and expensive process of serial synthesis and screening. In the search for more cost-effective methods of drug development, combinatorial chemistry has been readily adapted to the requirements of the medicinal chemist where it has occupied prime status for more than a decade. In essence, combinatorial chemistry involves the synthesis of large numbers of structurally related compounds either as mixtures in the same reaction or individually by parallel semi-automated synthesis. Several permutations and combinations enable the synthesis of hundreds to millions of analogues for biological screening\textsuperscript{1} in about the same time that traditional methodology would generate but a few. Two main approaches have been the split-mix (portioning-mixing) which involves splitting, coupling and combining of resin to generate libraries of thousands of compounds on just a few grams of resin, and the parallel approach wherein the library components are synthesized individually. Unfortunately however, the split-mix technique has been relegated to second-place strategy. Thus, parallel synthesis of small organic molecules has now been at the forefront of combinatorial chemistry wherein new molecules are synthesised as singles. Several techniques and instruments have been devised which invariably depend on insoluble polymer supports as the backbone. Traditionally, these insoluble polymer supports have been claimed as advantageous as it is easy to wash away the excess of reagents and cleave the product as and when desired. This technique is quite satisfactory, but with a few limitations, which include complete heterogeneity and thus, a large excess of reagents are needed to force the reaction. This is not a major drawback, if the reagents are not expensive and are not environmentally hazardous. The second and major drawback in this technique is that catalysed reactions have no major role to play in solid phase organic synthesis as the reaction conditions always require an excess of reagents. This limitation is more pronounced in the case of asymmetric catalysis and in hydrogenations where heterogeneous catalysts are very essential. To address these limitations and also to work more closely to classical solution phase organic synthesis, soluble polymer supports\textsuperscript{4} have been introduced and a vast amount of work has been documented in recent times. The differences between soluble and insoluble polymers are briefly summarized in Table I.

The general criteria for identifying a proper soluble polymer for performing the chemistry are that it should \( (a) \) be commercially available, \( (b) \) demonstrate good mechanical and chemical stability, \( (c) \) have

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Table 1 — Difference between soluble and insoluble polymers

<table>
<thead>
<tr>
<th>Insoluble polymers</th>
<th>Soluble polymers</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Generally polystyrene based with cross linkages.</td>
<td>1. Generally PEG based or Polystyrene based but without cross linkage.</td>
</tr>
<tr>
<td>2. Commonly used polymers include Merrifield, Wang, etc.</td>
<td>2. Commonly used polymers include PEG and Polyvinyl alcohol.</td>
</tr>
<tr>
<td>3. Reactions are always heterogeneous.</td>
<td>3. Reactions always homogeneous, but after the reaction, precipitation of the polymer can be achieved by the addition of a particular solvent.</td>
</tr>
<tr>
<td>4. Molecular weights are generally not mentioned and instead loading capacities are mentioned in millimoles.</td>
<td>4. Will have more precise average molecular weights.</td>
</tr>
<tr>
<td>5. Non linear kinetic behaviours and reagents are not exposed to full extent.</td>
<td>5. Linear kinetic behaviour and reagents are always exposed to reaction.</td>
</tr>
<tr>
<td>6. Excess reagents are always required to force the reaction to completion.</td>
<td>6. Generally stoichiometric reagents are sufficient to force the reaction to completion.</td>
</tr>
<tr>
<td>7. It is not possible to characterise the products by routine means and solid state and magic angle NMR spectroscopy required to characterise the progress of the reaction.</td>
<td>7. It is rather routine to characterise the products by usual NMR and mass spectroscopy.</td>
</tr>
</tbody>
</table>

Chart 1
appropriate arms for loading the small organic molecule or its precursor and be soluble in a given solvent.

A few polymers with the above properties have been identified and routinely used which include non-cross linked and cross-linked polymers derived from ethylene glycol, linear polystyrene and styrene acrylates besides others (Chart 1).

Of the several polymers studied in this area, it was demonstrated that polyethylene glycol (PEG) which is available commercially in different molecular weights was found to be practical due to its high solubilising and reprecipitating properties. Our laboratories have taken up a joint project to explore the possibility of utilising soluble polymers in asymmetric catalysis and address few limitations posed by insoluble polymers in this area of research activity. In this direction, a vast amount of literature dealing with the soluble polymer supported chemistry has been compiled. As the body of literature dealing with polymer chemistry is so enormous, some criteria have been imposed in compiling this particular review.

The present review thus deals with asymmetric synthesis in organic chemistry wherein only soluble polymers have been used as support (PEG in particular) for either the catalyst or substrate and only these reactions are included. However some of the reviews, which have appeared, recently have been cited for the benefit of the reader.

The classification of this review is based on a particular transformation and wherever applicable a comparative statement with reference to solution phase and insoluble support is also given.

A. Asymmetric dihydroxylation

There was a great need for catalytic systems for the asymmetric dihydroxylation (Scheme I) of olefins and Sharpless et al. have pioneered in developing the most versatile catalytic system comparable to any biological process with universal applications. This system comprised of catalytic OsO₄, chiral ligand (derived from Cinchona alkaloid) and stoichiometric oxidant NMO.

However, due to high cost of both cinchona based ligand and the osmium metal, methods for easy recovery of catalyst and ligand were of major interest. This is more so when this technology is applied on large scale. To address this issue, alkaloid derived ligands were immobilised initially on insoluble polymers with some success. Incidentally, PEG based ligand I was reported by Janda et al. for the first time for asymmetric dihydroxylation with some success in terms of ee's (Table II), even though the recovery of the ligand was achieved to greater than 98% by simple precipitation with diethyl ether. They were able to recycle the ligand without loss of significant enantiomeric excess when OsO₄ was added after each run (Scheme II).

The same group later observed that the MeO-PEG modified phthalazine 3 was very effective and diols were synthesised in optical purities of more than 96% ee's (Table III).

This chiral ligand on PEG worked successfully even on the substrates anchored on cross-linked insoluble polymers.

A further refinement to this process was reported by Bolm et al., wherein the ester linked PEG was replaced by an ether linked PEG 4, leading to excellent chiral induction for substrates such as trans-stilbene, trans-methyl styrene, styrene and trans-5-decene to afford the corresponding diols with very high enantiomeric excesses (>96% ee).

More recently, Structure Enantioselectivity Relationship (SER) studies by Zhang et al. revealed that a bi or tri cyclic planar aromatic group at the 9-O position of the alkaloid is necessary to achieve optimum enantioselectivity in the asymmetric dihydroxylation process. This led them to prepare the soluble polymer bound ligand 5.

![Scheme I](image-url)
a) TEA, DMAP, glutaric anhydride
b) DCC, DMAP, ROH

1. \( R = \text{PEG monomethyl ether} \)
2. \( R = \text{Ethyl} \)

**Scheme II**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Olefin</th>
<th>Oxidant</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>NMO</td>
<td>87</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>Ph-Me</td>
<td>K$_3$FeCN$_6$</td>
<td>88</td>
<td>98</td>
</tr>
<tr>
<td>1</td>
<td>Ph</td>
<td>NMO</td>
<td>87</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>K$_3$FeCN$_6$</td>
<td>83</td>
<td>99</td>
</tr>
<tr>
<td>1</td>
<td>Ph</td>
<td>NMO</td>
<td>98</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>K$_3$FeCN$_6$</td>
<td>95</td>
<td>99</td>
</tr>
<tr>
<td>1</td>
<td>n-Bu</td>
<td>NMO</td>
<td>84</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>n-Bu</td>
<td>K$_3$FeCN$_6$</td>
<td>80</td>
<td>97</td>
</tr>
</tbody>
</table>

The PEG used by these researchers has the average MW 5000 and was completely soluble in a tert-butanol - water mixture (1:1). The ee's obtained were comparable with the earlier work reported (Table IV).

**B. Asymmetric hydrogenations**

Even though asymmetric homogeneous catalysis is very successful in asymmetric hydrogenations, the major problem of recovering the catalyst and recycling was tedious. Though immobilising this homoge-
Table IV — Catalytic asymmetric dihydroxylation reactions using ligand 5

<table>
<thead>
<tr>
<th>Entry</th>
<th>Olefin</th>
<th>Temp (°C)</th>
<th>Time (hr)</th>
<th>Yield (%)</th>
<th>ee(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>0</td>
<td>18</td>
<td>93</td>
<td>98 (99.88)</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>0</td>
<td>24</td>
<td>87</td>
<td>82 (98.60)</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>0</td>
<td>24</td>
<td>89</td>
<td>79 (94)</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>0</td>
<td>24</td>
<td>92</td>
<td>90 (91)</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>r.t.</td>
<td>30</td>
<td>81</td>
<td>96</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>r.t.</td>
<td>30</td>
<td>83</td>
<td>93 (97)</td>
</tr>
</tbody>
</table>

Values in parenthesis indicate yields in solution

efficient in the asymmetric reduction of olefins and ee’s were in the range of 88% to 94%, as represented in the synthesis of Naproxen (Scheme IV).

The same research group went on to load other homogeneous catalysts including BINAP and Pyrophos on PEG monomethyl ether.

The catalyst MeO-PEG-supported BINAP 8 was prepared\[17,18\] by the condensation of 5,5’ diamino BINAP with terephthaloyl chloride in presence of triethylamine followed by reaction with MeO-PEG-OH (molecular weight 5000). This ligand in combination with [RuCl2(cymene)]2 generated the catalyst 9 (Scheme V).

Similarly, the Ru(BINAP)(acac)2 based catalyst 10, was loaded on PEG to yield catalyst 11 which asymmetrically reduced the double bond of 2-(6’-methoxy-2'-naphthyl)-propenoic acid with excellent conversion (100%) and ee (90.2%) with recovery of the catalyst with great ease and without loss of activity (Scheme VI).

C. Asymmetric reduction of prochiral ketones

The oxazaborolidine catalysed reduction of ketones by borane\[19\] is a popularly used reaction which yields the corresponding chiral secondary alcohols in high ee’s (Scheme VII). In order to avoid the competing non-catalysed reaction, catalyst concentration of about 1-20% has to be employed to ensure high ee’s. To allow for easy recycling of this rather expensive catalyst, several modifications have been attempted which include attaching this catalyst to a polystyrene gel\[20\]. Through this approach even though the catalyst was recycled efficiently, the catalyst turn-over number could not be increased.

A more systematic approach by Kragl et al\[21\] involved in the preparation of soluble polymer supported oxazaborolidine 12 by polymerisation of styrene grafted α, α-diphenyl tyrosinol\[22\] (Scheme VIII).

Similarly, α, α diphenyl prolinol was also reacted with the polymer bound boronic acid to prepare the catalyst 13 and aralkylketones were reduced to chiral alcohols with 84-99% ee depending on the substitution patterns (Scheme IX).

These catalyst systems were very efficient of experimental set-up for the continuous catalysis experiments in cells with nanofiltration membranes. The same research group has loaded the CBS reagent on polymer enlarged homogeneously
5, 5'- Diamino BINAP + \[\text{aligned chemical structure}\]  

Scheme III

Catalyst (7) \[\text{aligned chemical structure}\]

Scheme IV

Polyamide oligmer \[\text{aligned chemical structure}\]

Scheme V — Synthesis of MeO-PEG supported [RuCl(BINA)(cymene)]Cl
Scheme VI

Scheme VII

Scheme VIII
soluble methylhydrosiloxanedimethylsiloxane co-polymer (15%) and obtained 14 with comparable results (Scheme X, Table V).

PEG supported bisoxazolines for catalytic enantioselective reactions

Chiral bis-oxazolines\textsuperscript{23} have found wide applicability in catalytic asymmetric synthesis including asymmetric Diels-Alder reaction, cyclopropanation, ene reaction besides others. Cozzi \textit{et al}\textsuperscript{24}, were the first to immobilise these bisoxazoline catalysts on PEG and studied some asymmetric transformations. The strategy adopted by this group is as follows.

4-O-Benzyl and 4-O-allyl benzyl bromides 1, 2 were used to alkylate the lithium enolate of dimethyl methyl malonate which were then transformed by standard procedures into the corresponding diacid chlorides (Scheme XI). Amidation with chiral
Table V — Enantioselective reduction of various ketones using 10% cat.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Ketones</th>
<th>Yield (%)</th>
<th>ee (%)</th>
<th>Config</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14a</td>
<td>PhCOCH₂</td>
<td>86</td>
<td>97</td>
<td>R</td>
</tr>
<tr>
<td>2</td>
<td>14b</td>
<td>PhCOCH₂</td>
<td>89</td>
<td>98</td>
<td>R</td>
</tr>
<tr>
<td>3</td>
<td>14a</td>
<td>PhCOCH₂</td>
<td>88</td>
<td>89</td>
<td>R</td>
</tr>
<tr>
<td>4</td>
<td>14b</td>
<td>PhCOCH₂</td>
<td>83</td>
<td>94</td>
<td>S</td>
</tr>
</tbody>
</table>

These ligands thus obtained were tested for asymmetric Diels Alder reaction in presence of Cu(OTf)₂ with good chemical yield (83%) but with lesser ee's (45%, Scheme XII). However, cyclopropanation induced by the same system on styrene diazoacetate yielded the cyclopropane derivative in more than 93% ee which is comparable with solution phase chemistry (Scheme XIII). In the case of ene reaction between methylene cyclohexane and ethyl glyoxalate, the product was obtained with 91% ee whereas the same reaction in the classical solution method has also given similar results as reported by Evans et al. (Scheme XIV).

Glos and Reiser have also synthesised these bisoxazolidine ligands on PEG 5000 and studied the asymmetric cyclopropanation and palladium catalysed allylic alkylation. The strategy involved initial aminoalcohols, tosylation and oxazoline ring closure promoted by DMAP yielded the bisoxazolines. The phenol was deprotected and loaded onto PEG through linker as shown in the Scheme XI to get the ligands 15 and 16.
syntheses of chiral bisoxazolines connected by nitrogen, unlike the carbon linkage reported by Cozzi et al.\textsuperscript{21}, and were loaded on MeOPEGCH\textsubscript{2}OH through 1,4-benzyl linkage 17 (Scheme XV). This ligand was used in C-C bond formation of allylacetae catalysed by \([\text{Pd(allyl)Cl}][\text{]} to yield the allyl substituted product in 95\% to 97\% ee (Scheme XVI).

Similarly Cu(OTf)\textsubscript{2} catalysed cyclopropanation of styrene with methyl diazoacetate yielded cyclopropyl carboxyl ester albeit in moderate de's (7:3 in favour of trans) but in good ee (87\%) (Scheme XVII).

**Enantioselective epoxidation of olefins**

The Jacobsen epoxidation has recently emerged as a powerful tool for the asymmetric epoxidation of un-functionalised olefins\textsuperscript{26}. This reaction is catalysed by structurally simple Mn(III)-salen complexes 18 and has been optimised in terms of the catalyst structure and choice of stoichiometric oxidants. Immediately after this discovery, several publications have appeared in literature wherein the Salen ligand has been heterogenised as a means to recycle the chiral catalyst via zeolites, clay, siloxane membrane\textsuperscript{27} and also by grafting onto inorganic supports\textsuperscript{28}. Other approaches for recycling the catalyst were copolymerisation of functionalised Salen monomer\textsuperscript{29} or attachment to already existing polymer. All the above strategies were successful to a great extent. Janda’s group once
again has taken the lead and were able to study, in detail, the effect of various polymers and a comparative study has been published in full\textsuperscript{[10]}. The salen-Mn complex was loaded onto MeO-PEG 5000, non cross linked polystyrene (NCPS), JandaGel resin and also as methyl ester to prepare catalysts 19 to 23 through carboxyl linker. This study has revealed that the ee’s (Table VI) obtained were comparable and no marked differences were observed in the epoxidation of unfunctionalised olefins (Scheme XVIII). The recyclability of the catalyst was also identical and could not be recycled for more than 3 times.

Poly-salen-Mn(III)complexes 24 and 25 have been developed by Zheng et al\textsuperscript{[31]}, but the ee’s and yields were moderate (Scheme XIX). The epoxidation reactions catalysed by the poly-salen complexes were carried out in dichloromethane and styrene being used initially as model substrate. In most of the runs, the complexes were degraded and low enantioselectivities and yields were observed.

### Table VI — Epoxidation result for different (Salen) Mn catalysts

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>ee(%)</th>
<th>Yield(%)</th>
<th>ee(%)</th>
<th>Yield(%)</th>
<th>ee(%)</th>
<th>Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>52</td>
<td>82</td>
<td>88</td>
<td>79</td>
<td>76</td>
<td>70</td>
</tr>
<tr>
<td>20</td>
<td>51</td>
<td>76</td>
<td>90</td>
<td>79</td>
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</tr>
<tr>
<td>21</td>
<td>51</td>
<td>81</td>
<td>88</td>
<td>77</td>
<td>79</td>
<td>71</td>
</tr>
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<td>22</td>
<td>35</td>
<td>61</td>
<td>86</td>
<td>75</td>
<td>78</td>
<td>69</td>
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<td>23</td>
<td>52</td>
<td>82</td>
<td>87</td>
<td>80</td>
<td>84</td>
<td>75</td>
</tr>
</tbody>
</table>

#### Asymmetric epoxidation of \(\alpha, \beta\) unsaturated ketones

The polyamino catalysed asymmetric epoxidation of chalcones discovered by Julia and Colonna (Scheme XX) is a powerful tool in synthetic organic chemistry\textsuperscript{[10]}. The chiral polyamino acids generally remain insoluble and thus are heterogeneous in nature. Roberts et al\textsuperscript{[33]} have for the first time synthesised the soluble version of Julia-Colonna catalysts 26-29 thus demonstrating its utility in liquid phase synthetic technologies. Diamino PEG (MW3350) was utilised as the anchor for few polyleucines and subjected to epoxidation of chalcone. The ee’s were in the range of 95-98\% based on the percentage of conversion (Scheme XXI).

#### Catalytic enantioselective Mukaiyama reaction

Salvadori et al\textsuperscript{[35]} have developed a soluble copolymer P1 30 between styrene, divinyl benzene and the enantiomerically pure salicylaldimine ligand. The Lewis acid prepared from this macromolecular chiral ligand and Ti(OiPr)\textsubscript{4} has been used (Scheme XXII) in the catalytic Mukaiyama reaction. The limitations of this
study was that at 48% conversion, the product was optically enriched to the extent of only 53%.

Conclusions
We have presented in this review, some of the recent contributions in the area of asymmetric catalysis and its applications especially supported on poly ethylene glycol. The methodologies provide alternative strategies for recycling the catalysts and optical enrichments over the more commonly utilised insoluble polymers in combinatorial chemistry. It is quite apparent from this review that only a small number of publications have appeared using this technique and there is enough scope to exploit the usefulness of PEG in asymmetric catalysis. This is more so to attach substrates onto the PEG
support(soluble polymer) and study the level of optical inductions which is reverse of the reports wherein the catalysts are loaded onto the PEG. As polymers are known to play a role in the reactivity of the substrates loaded, it may be desirable to tailor make the polymers for performing this chemistry. To this end, the authors have initiated some efforts.

Acknowledgement

The investigators are thankful to IFCPAR for a research grant 2305-1.

References

3. PEG is available from Aldrich Co, with various Molecular Weights.
4. The project is funded by IFCPAR no 2305/1.
10. Both chiral reagents are commercially available from M/S Aldrich by name AD-mix-α and AD-mix-β.